



Kidney Injury after Chemotherapy

By

Mostafa Abdel_Elsalam
Mansura University

Case scenario

- Female patient, 37 years old
- Undergo surgery for osteosarcoma
- Received one cycle of adriamycin and cisplatin
- Presented with Cr=5.4mg/dl, Hb=9gm/dl, uric acid=11mg/dl
- When to start the next session

Why is the Nephrologist called?

- Kidney disease either pre existing or developing in the course of the cancer
- New Glomerular paraneoplastic disease
- Obstructive Nephropathy
- Tubular interstitial Damage
- Thrombotic microangiopathy
- Radiation Nephropathy
- Tumor invasion of the kidney
- Tumor lysis syndrome
- Multiple Myeloma
- Fluid and electrolyte disorders
- Decision regarding renal replacement therapy

GFR reduction and cancer risk?

- During a median follow up around 13 years, 370 cancer deaths were observed in study cohort.
- For every 10-mL/min/1.73m² reduction in eGFR, there was an increase in cancer-specific mortality of 18% in the fully adjusted model.
- This excess cancer mortality varied with site, with the greatest risk for **breast and urinary tract cancer deaths**

Iff S et al. Reduced estimated GFR and cancer mortality. AJKD 2013 in press.

Table 2. Categories of Chemotherapy-Induced Renal Toxicity

Tubulopathies

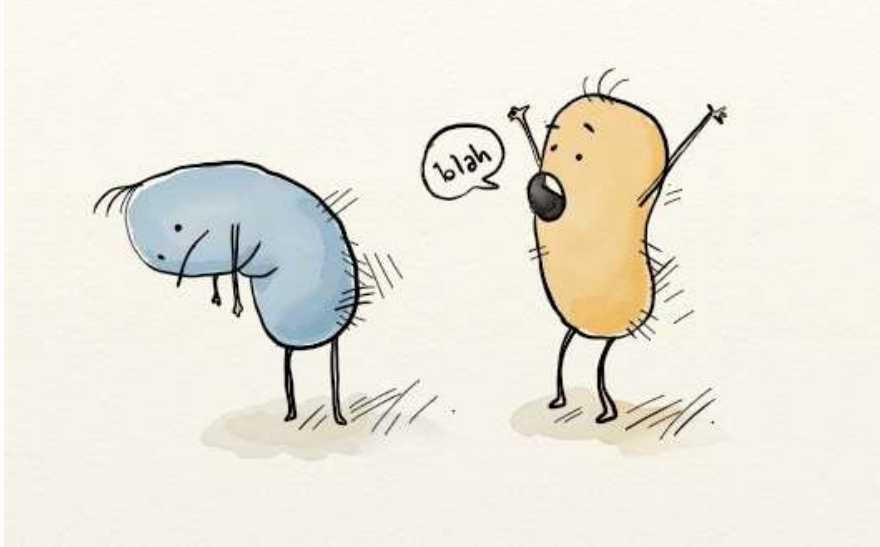
- FS
 - Cisplatin, ifosfamide, azacitadine, Diaziquone, imatinib, gefitinib
- Salt wasting
 - Cisplatin, azacitidine
- Magnesium wasting
 - Cisplatin, cetuximab, panitumumab
- NDI
 - Cisplatin, ifosfamide
- Syndrome of inappropriate antidiuretic hormone
 - Cyclophosphamide, vincristine

AKI

- Prerenal kidney injury (capillary leak syndrome)
 - Interleukin-2, denileukin diftitox
- Acute tubular necrosis
 - Platinums, zoledronate, ifosfamide, mithramycin
 - Pentostatin, imatinib, diaziquone
- Crystal nephropathy
 - MTX
- Thrombotic microangiopathy
 - Mitomycin C, gemcitabine
- Nephritic/nephrotic syndromes
 - Thrombotic microangiopathy
 - Anti-angiogenesis agents, mitomycin C, gemcitabine
 - Minimal change disease
 - Interferon, pamidronate
- FSGS
 - Interferon, pamidronate

CKD

- Chronic interstitial nephritis
 - Nitrosureas, cisplatin, MTX
- Glomerulosclerosis
 - Nitrosureas



Risk factors for chemotherapy-induced nephrotoxicity

Age Gender
Medical history
Genetics

Tumor-related kidney effects

direct renal involvement

myeloma-related
kidney injury

renal infiltration
(lymphoma and
leukemia)

urinary
obstruction

neoplasia-
associated
glomerulopathies

indirect renal involvement

true volume
depletion (N/V,
diarrhea, and
overdiuresis)

Effective volume
depletion
(cardiomyopathy,
malignant
ascites, and
pleural effusions)

metabolic effects
(hyperuricemia
and
hypercalcemia)

Innate drug
toxicity

high-dose drug exposure and prolonged course of therapy

insoluble drug or metabolite form crystals within intratubular lumens

potent direct nephrotoxic effects of the drug or toxin

drug combinations enhance nephrotoxicity
NSAIDs, aminoglycosides, and radiocontrast

Patient factors

older age

underlying
AKI or CKD

immune
response
genes

increased
allergic
reactions
to drugs

Patient factors

pharmacogenetics
favoring
drug/toxin toxicity

gene mutations in
hepatic and renal
CYP450

enzyme systems

gene mutations in
transport proteins
and renal
transporters

- Renal drug handling
- high blood (and drug) delivery rate to the kidneys
- proximal tubular uptake of toxins
- apical tubular uptake by endocytosis or another pathway
- basolateral tubular transport through OAT and OCT pathways
- relatively hypoxic renal environment
- high metabolic rate of tubular cells in the loop of Henle
- increased drug/toxin concentration in renal medulla and interstitium
- biotransformation of substances to ROS causing oxidative stress

Box 31.1 Common Causes of Kidney Injury in Cancer Patients

Prerenal

Hypovolemia (poor fluid intake, vomiting, diarrhea, capillary leak syndrome with IL-2)

NSAIDs

Hypercalcemia

Hepatorenal syndrome (after HCT, massive infiltration by cancer cells)

Intrarenal

Glomerular

Membranous nephropathy

ANCA vasculitis

Amyloidosis

Light chain deposition disease

Collapsing glomerulopathy (pamidronate)

Tubulointerstitial

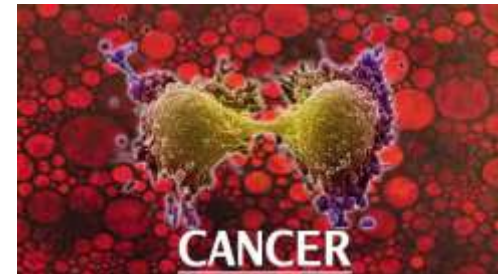
ATN due to sepsis, hypovolemia, IV contrast

ATN due to drugs (cisplatin, ifosfamide, zoledronate)

Acute cast nephropathy (myeloma)*

Tumor lysis syndrome (uric acid and calcium-phosphate deposition)*

Methotrexate*



Vascular

HUS/TTP (gemcitabine, mitomycin C, and other drugs; conditioning regimen for allogeneic HCT)

Postrenal

Obstruction of both urinary tracts by urological and nonurological cancers

Retroperitoneal fibrosis

Other

Bilateral nephrectomy (renal cancer)

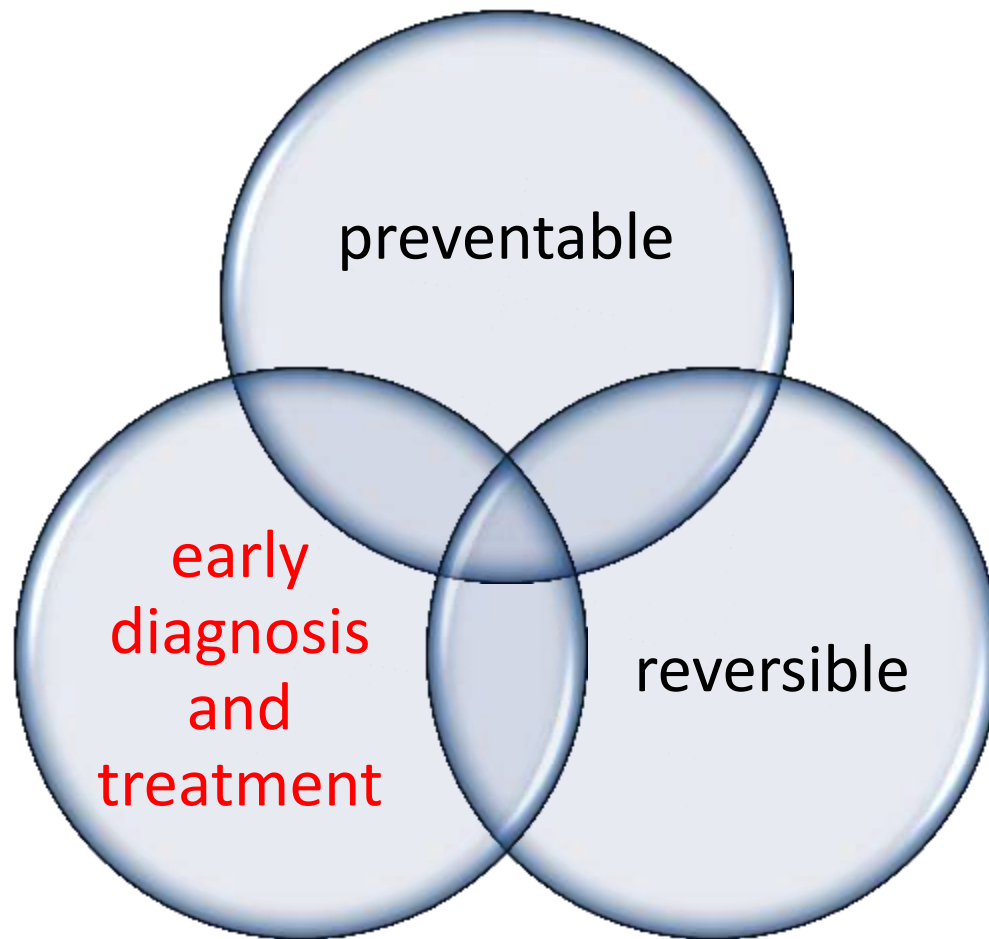
Massive infiltration of kidneys by lymphoma

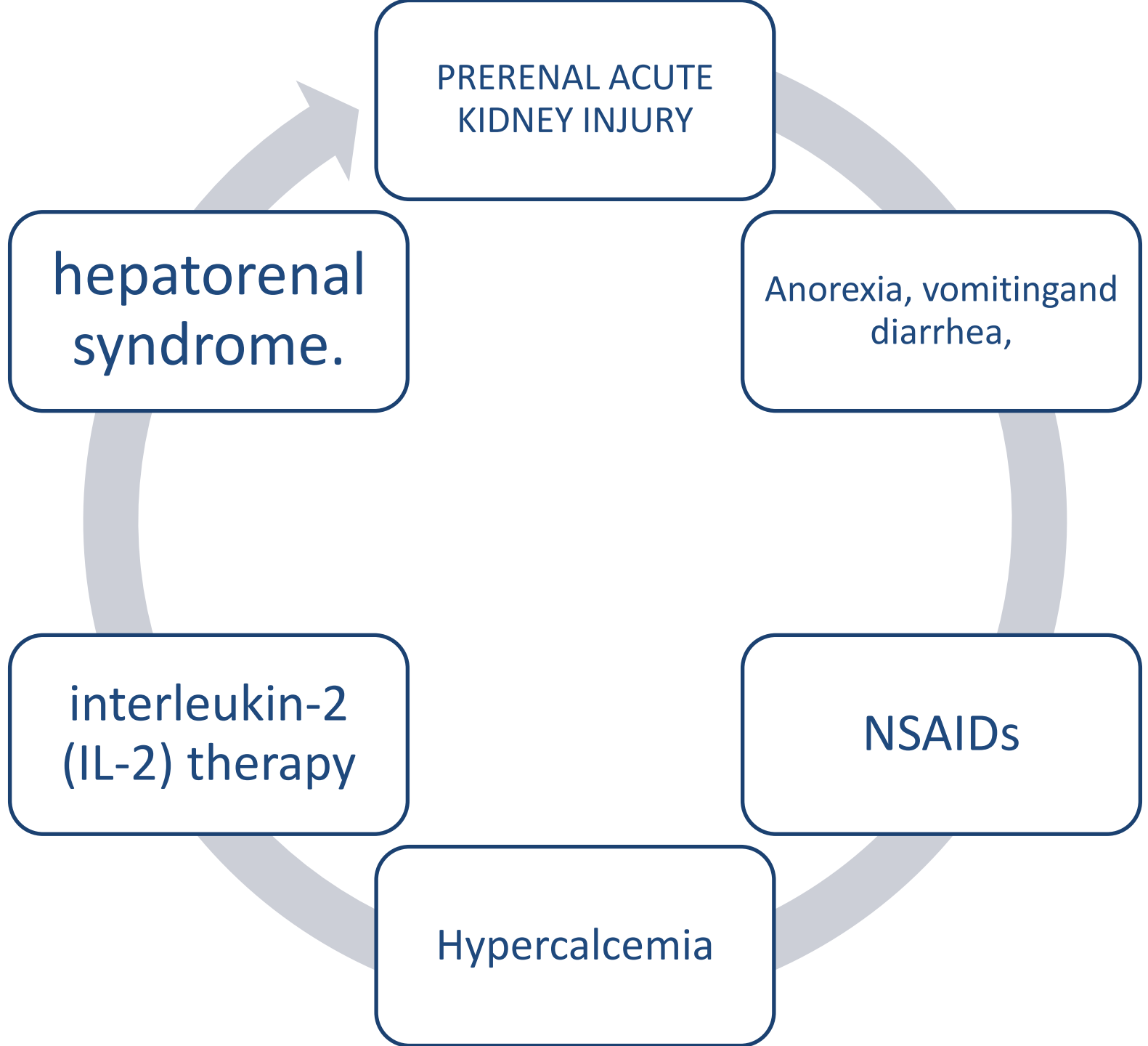
National Kidney Foundation's
**PRIMER ON
KIDNEY DISEASES**

acute kidney injury (AKI)

chronic kidney disease (CKD)

disorders of electrolyte and water balance..







HYPERCALCEMIA

common

lung cancer

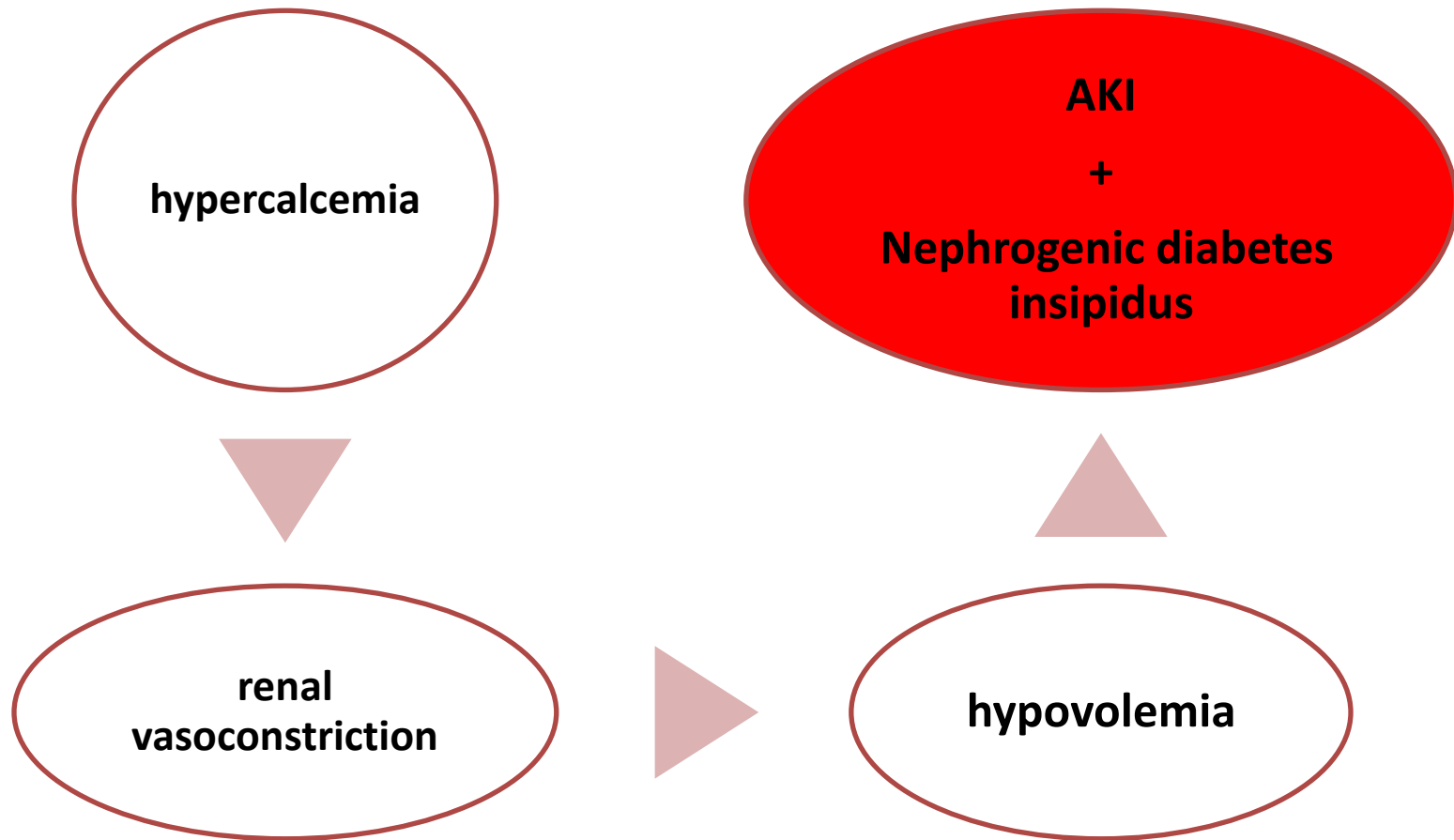
breast cancer and
multiple
myeloma

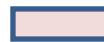
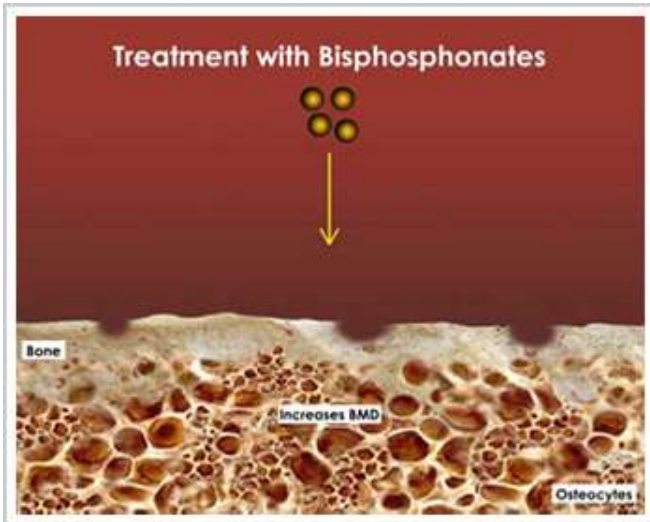


(PTHrp)

bone
breakdown

renal tubular
calcium
reabsorption

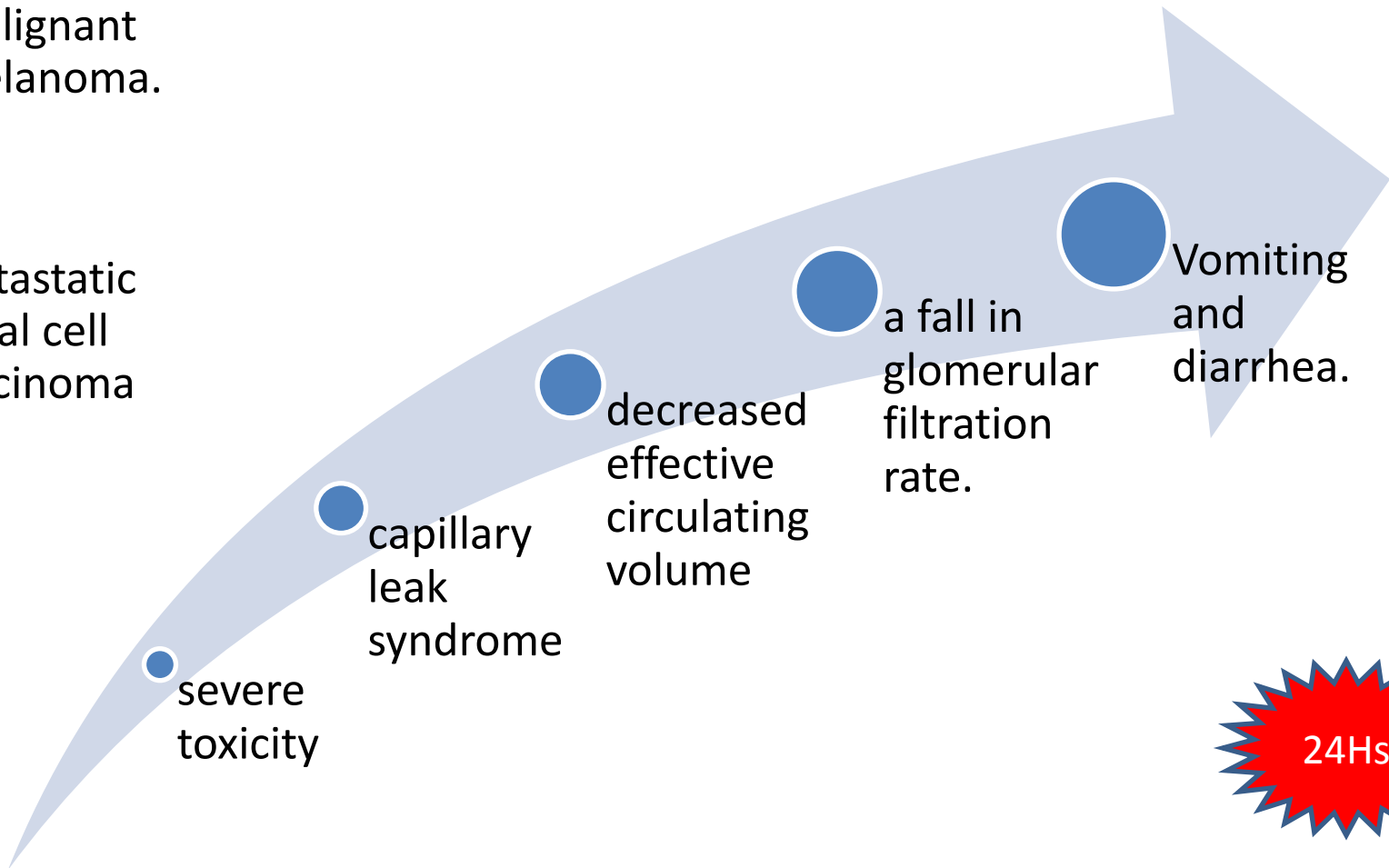




INTERLEUKIN-2

metastatic
malignant
melanoma.

metastatic
renal cell
carcinoma





HEPATORENAL SYNDROME



Massive infiltration of the liver by neoplastic cells.



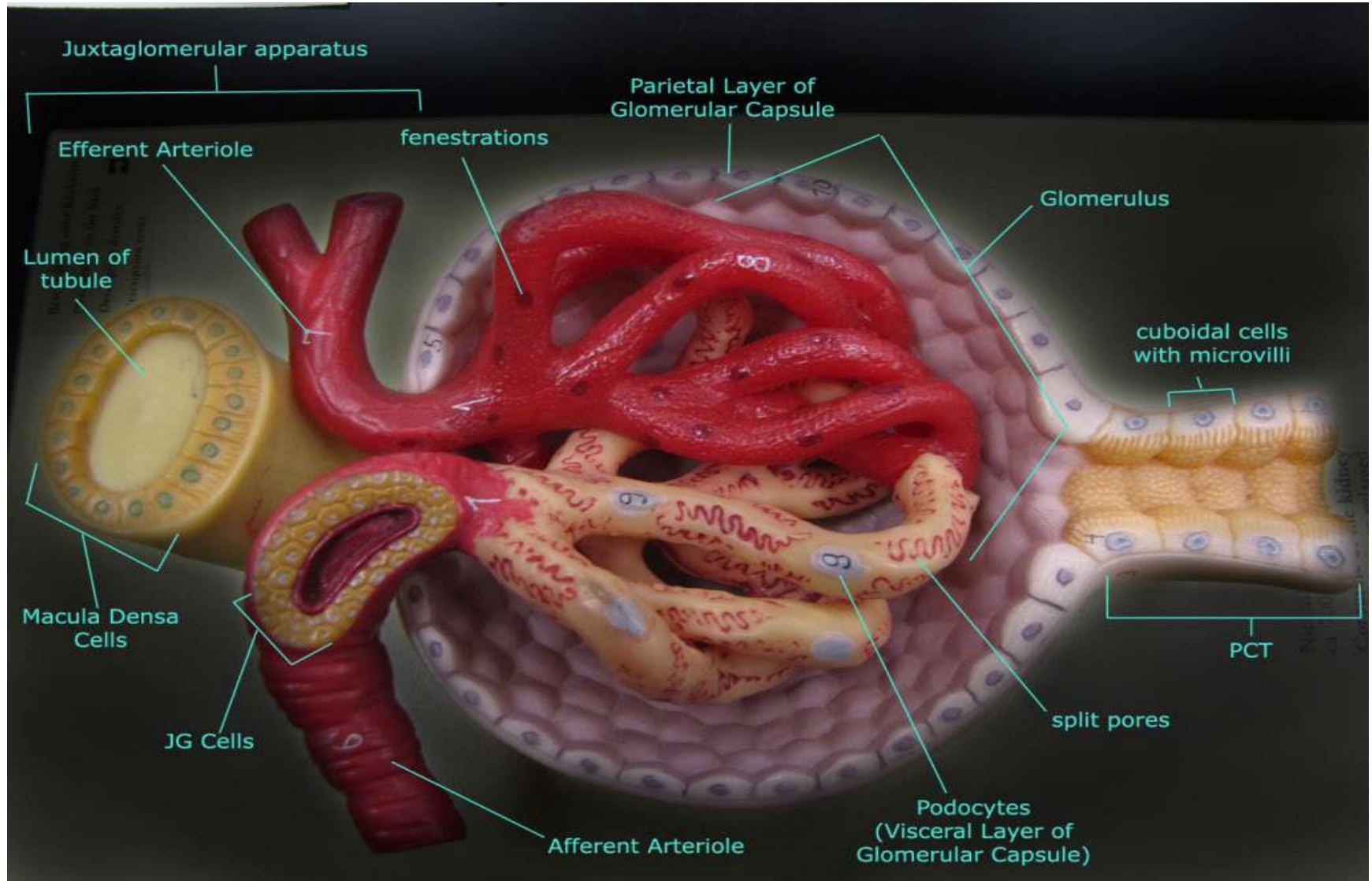
Acute severe hepatitis



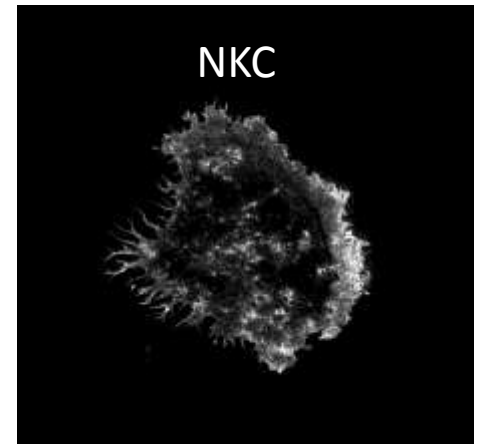
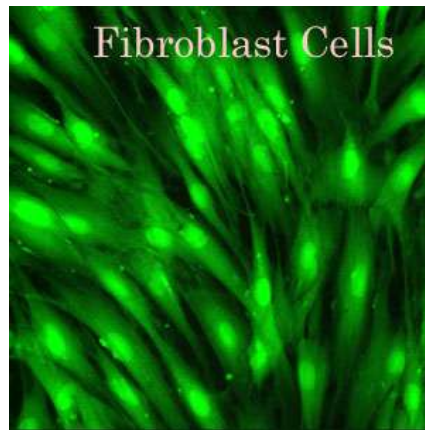
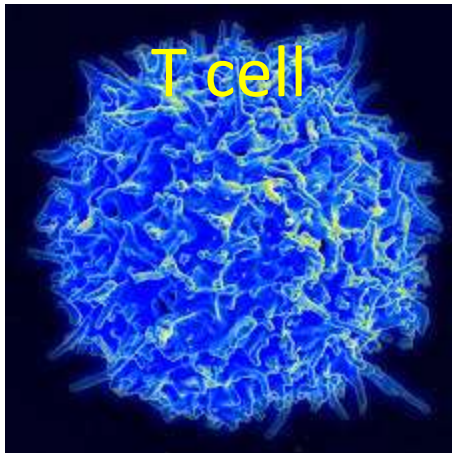
Tyrosine kinase inhibitors such as erlotinib.

INTRARENAL AKI

GLOMERULAR DISEASES



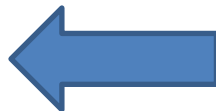
Podocytopathy



IFN



Infection



Malignancy

The most commonly used agent is IFN-a, which is used to treat hepatitis C and B viruses and various malignancies. IFN-b is used to treat multiple sclerosis, whereas IFN-g was studied as a treatment for chronic granulomatous disease.



Chronic IFN therapy

podocyte injury.

minimal change disease

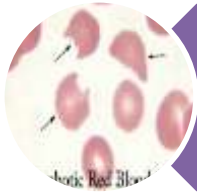
Nephrotic syndrome

complete remission was noted in all patients, with discontinuation of IFN



VASCULAR DISEASES

HUS/TTP



cancer itself



treatment



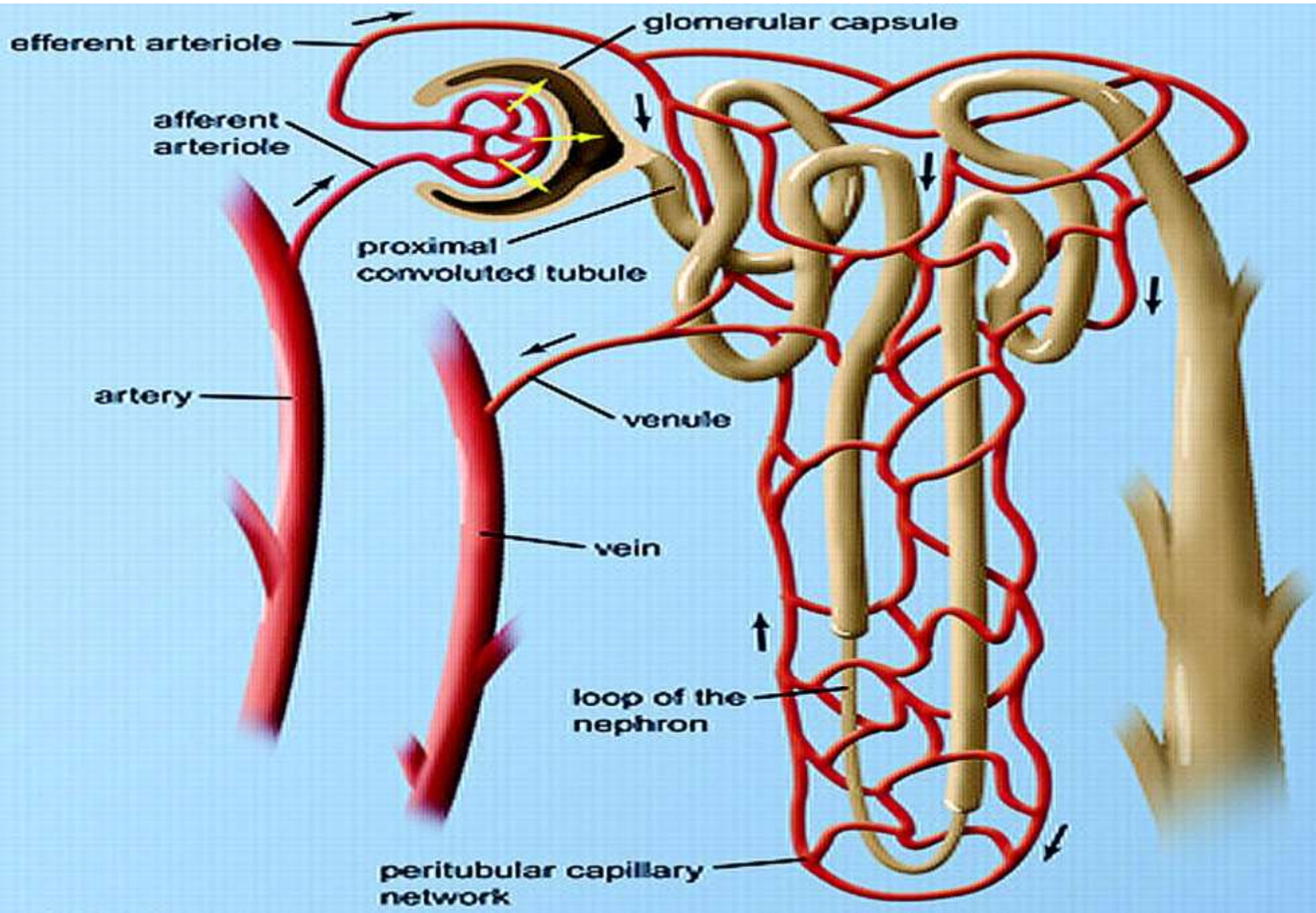
mitomycin C, gemcitabine,
bleomycin, and cisplatin

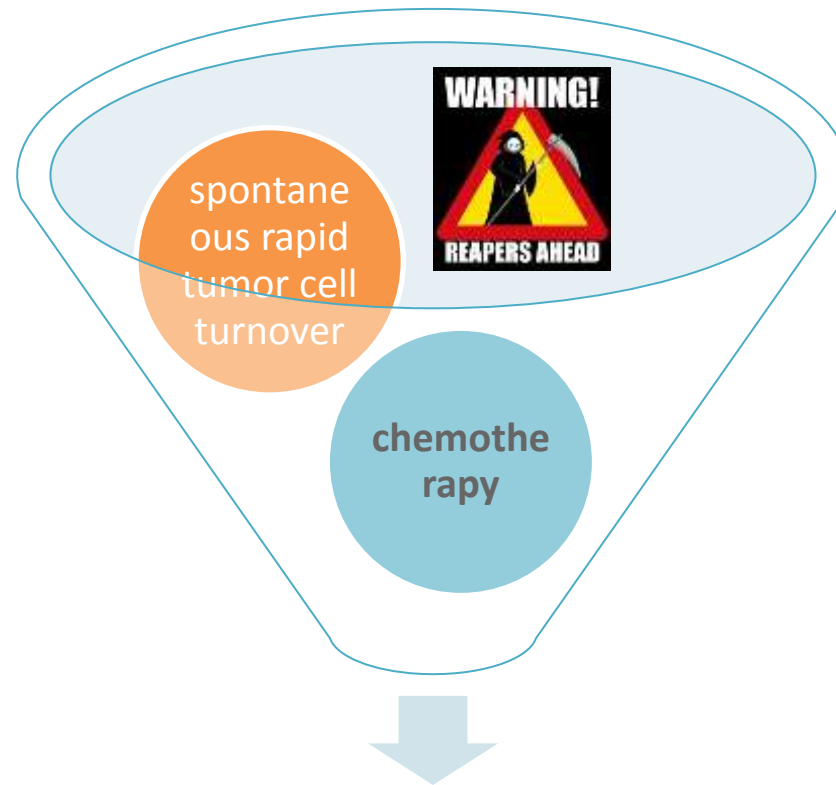


VEGF



Tubulointerstitial





TUMOR LYSIS SYNDROME

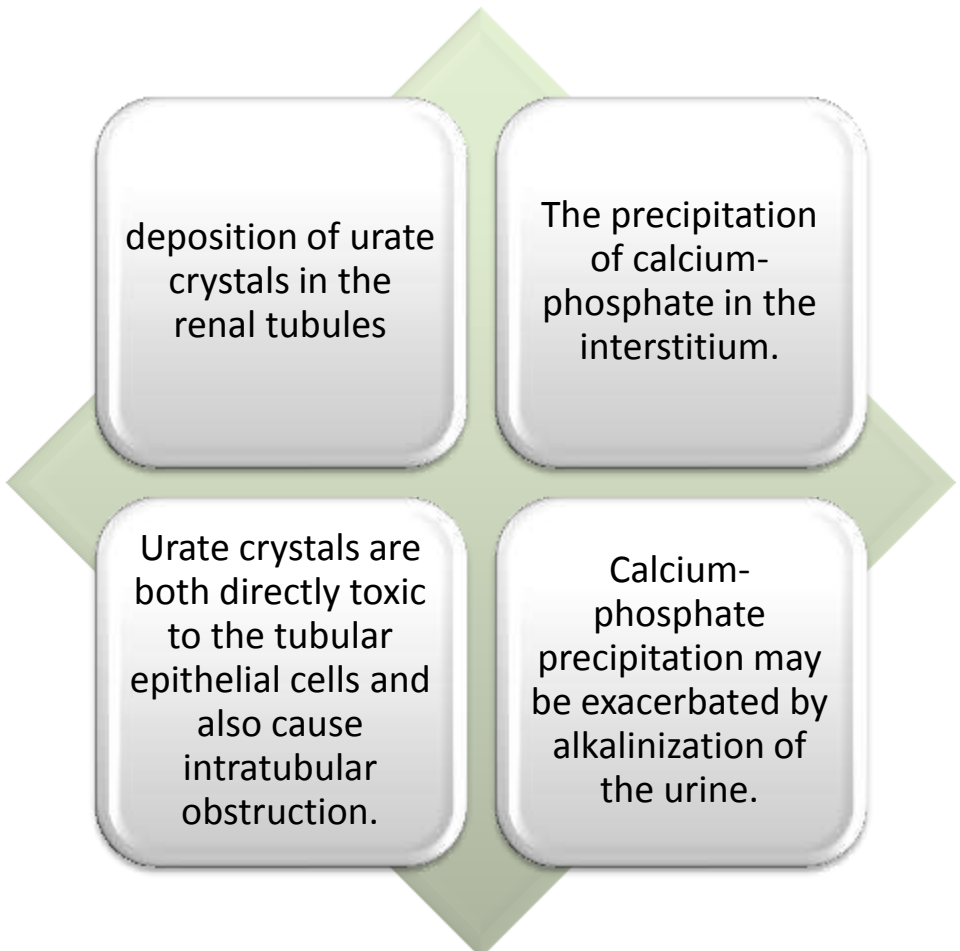


hyperuricemia

Hyperphosphatemia

Hypocalcemia

Hyperkalemia



deposition of urate
crystals in the
renal tubules

The precipitation
of calcium-
phosphate in the
interstitium.

Urate crystals are
both directly toxic
to the tubular
epithelial cells and
also cause
intratubular
obstruction.

Calcium-
phosphate
precipitation may
be exacerbated by
alkalinization of
the urine.

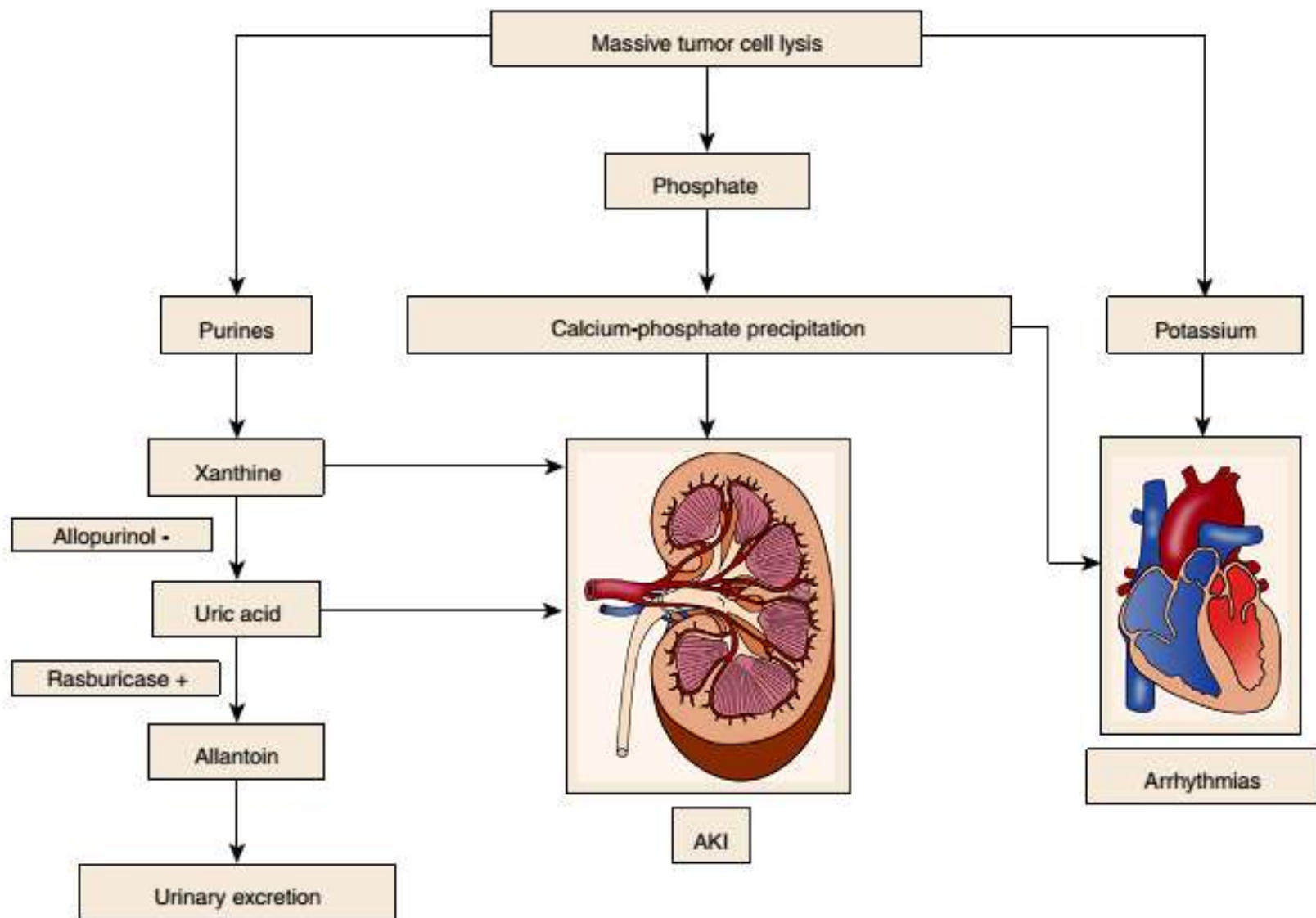


Figure 31.2 The two major mechanisms causing acute kidney injury (AKI) in tumor lysis syndrome are the deposition of urate crystals in the lumina of renal tubules and the precipitation of calcium-phosphate in the interstitium. Hyperkalemia may lead to the development of arrhythmias.



electrolyte
abnormalities

administration
of rasburicase

diuresis.

hemodialysis or
hemofiltration

hope

BISPHOSPHONATE-INDUCED KIDNEY DISEASE

- nephrotic syndrome and kidney dysfunction while receiving pamidronate; histology showed collapsing glomerulopathy with varying degrees of tubular injury.

- developed kidney failure. Severe tubular injury, which is not always reversible, has been reported with zoledronate.



supratherapeutic



lower GFR



normal saline



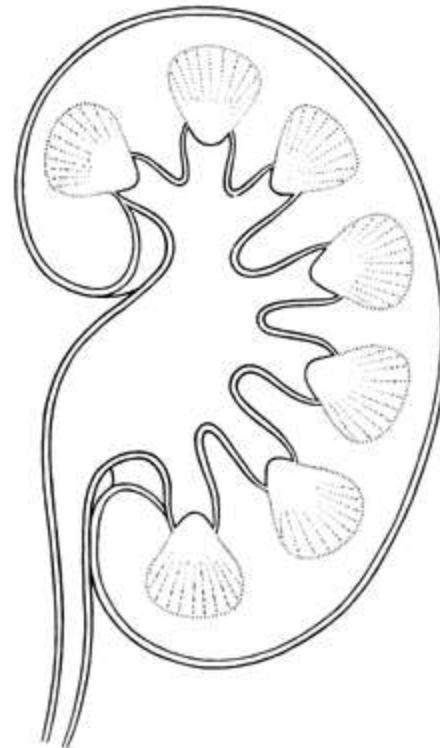
creatinine and
proteinuria



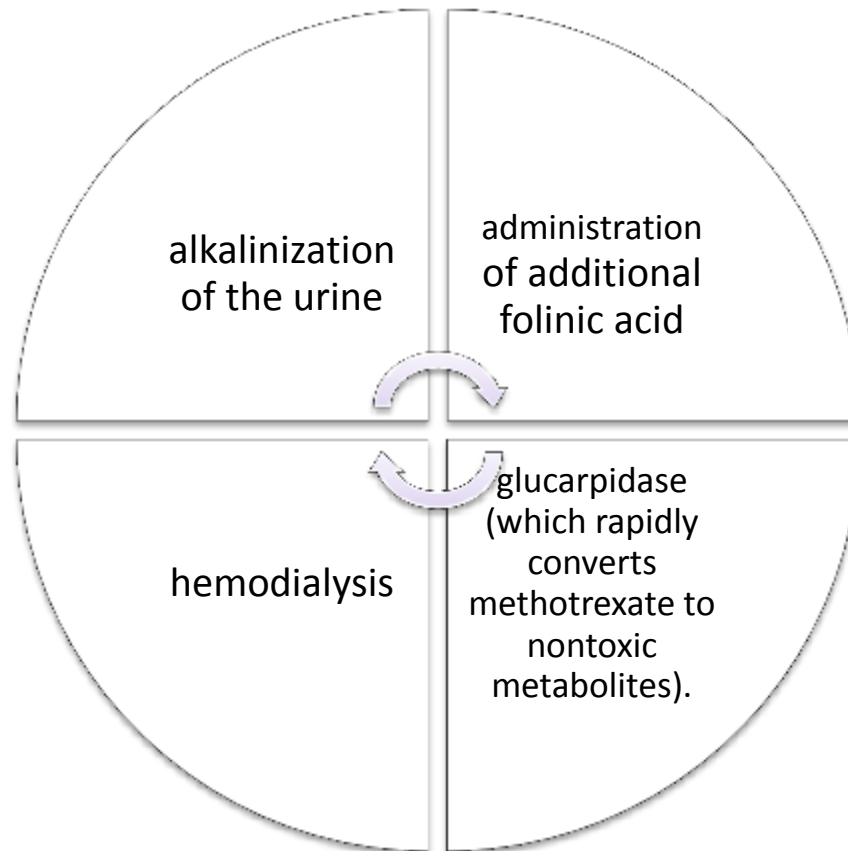
nephrotoxins



- METHOTREXATE
- leukemia, lymphoma, and less commonly, solid organ cancers.



- direct toxic effects on renal tubular cells a
- precipitation of the drug and its metabolites within the tubular lumen.
- Intraluminal crystallization is exacerbated by lower urine pH.
- Other factors associated with development of nephrotoxicity include preexisting kidney disease, concomitant use of other nephrotoxic drugs, hypovolemia, and higher plasma concentrations of the drug at 72 hours postinfusion.

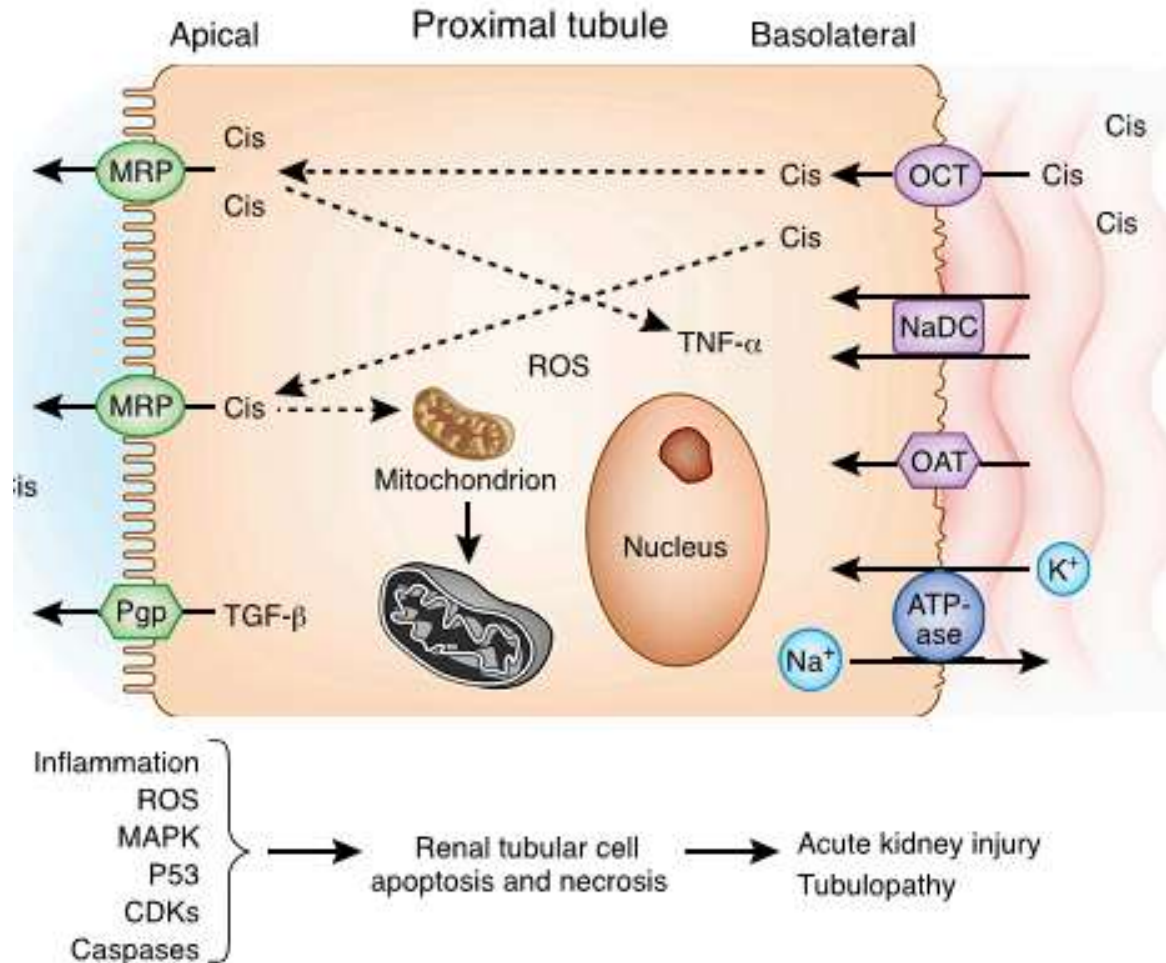


CISPLATIN



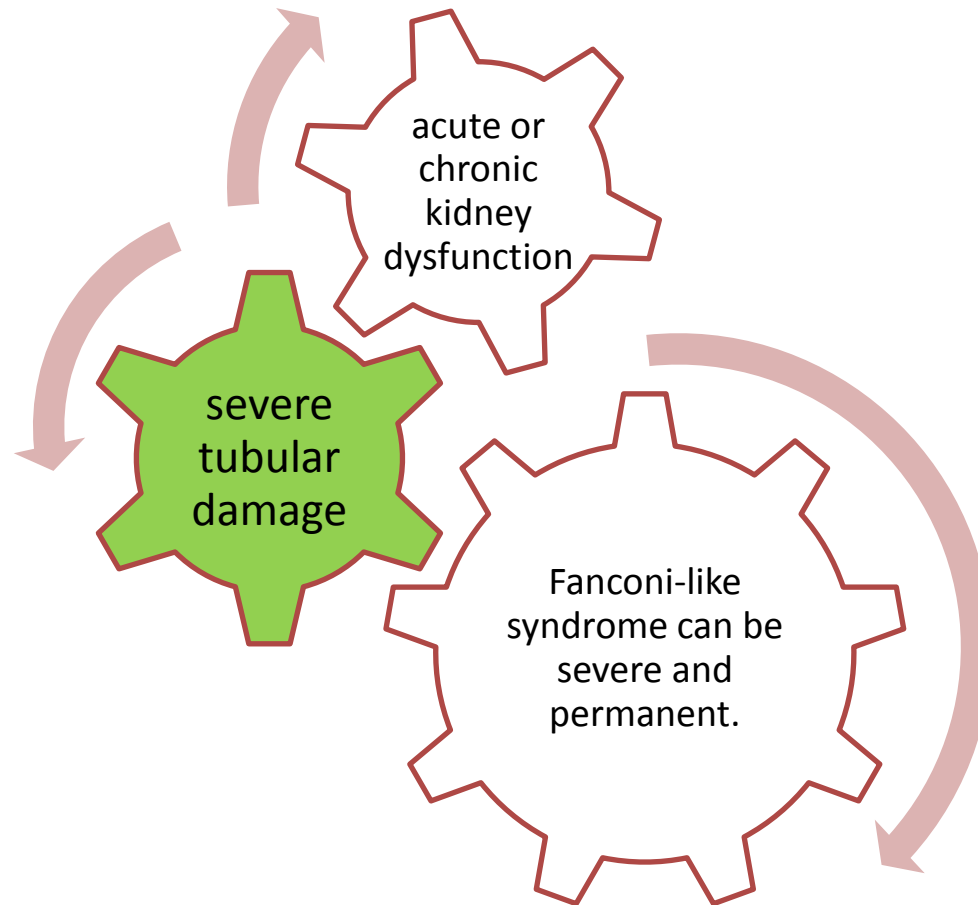
solid organ malignancies

CISPLATIN



Cisplatin (Cis) nephrotoxicity is, in part, related to its uptake by proximal tubular cells. Cis enters cells through organic cation transporters (OCTs), and when it accumulates within cells, it causes cell injury through multiple mechanisms. Apoptosis and necrosis of tubular cells result and cause clinical AKI and tubulopathy. CDKs, cyclin-dependent kinases; MAPK, mitogen-activated protein kinase; MRP, multidrugresistant protein; NaDC, sodium dicarboxylate; OAT, organic anion transporter; P53, protein 53; Pgp, P glycoprotein; ROS, reactive oxygen species.

IFOSFAMIDE



Gemcitabine

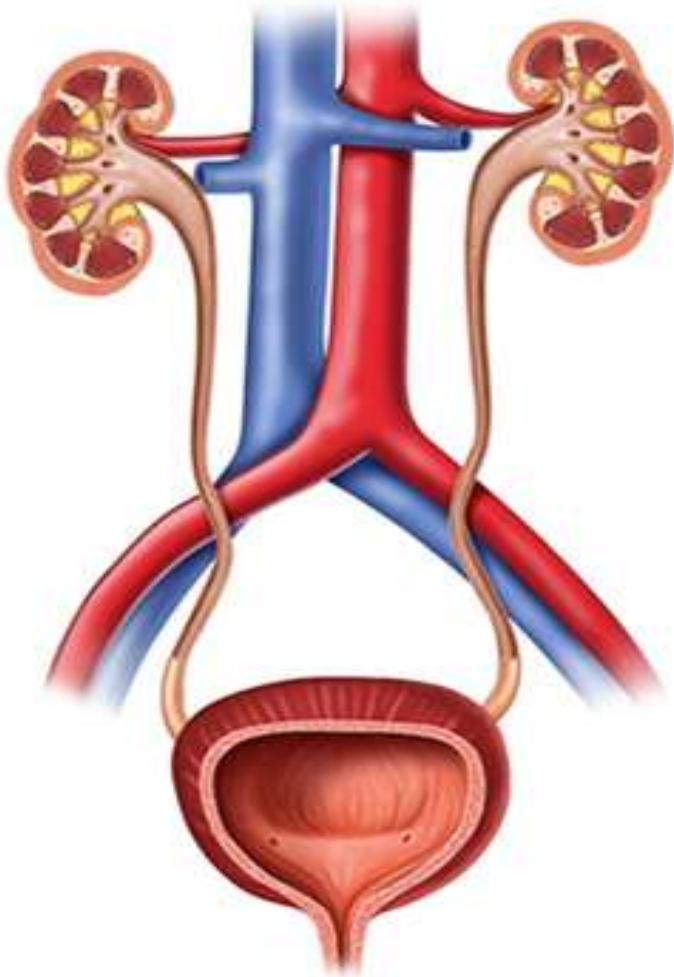
- Gemcitabine is a nucleoside analog with antineoplastic activity against a variety of solid tumors including pancreatic, non-small cell lung, bladder, ovarian and breast carcinomas
- Mild proteinuria and microscopic hematuria may occur in up to 50% of pt treat with Gemcitabine
- HUS is a well-described complication with an incidence of 0.31%-0.4%

OTHER DRUGS

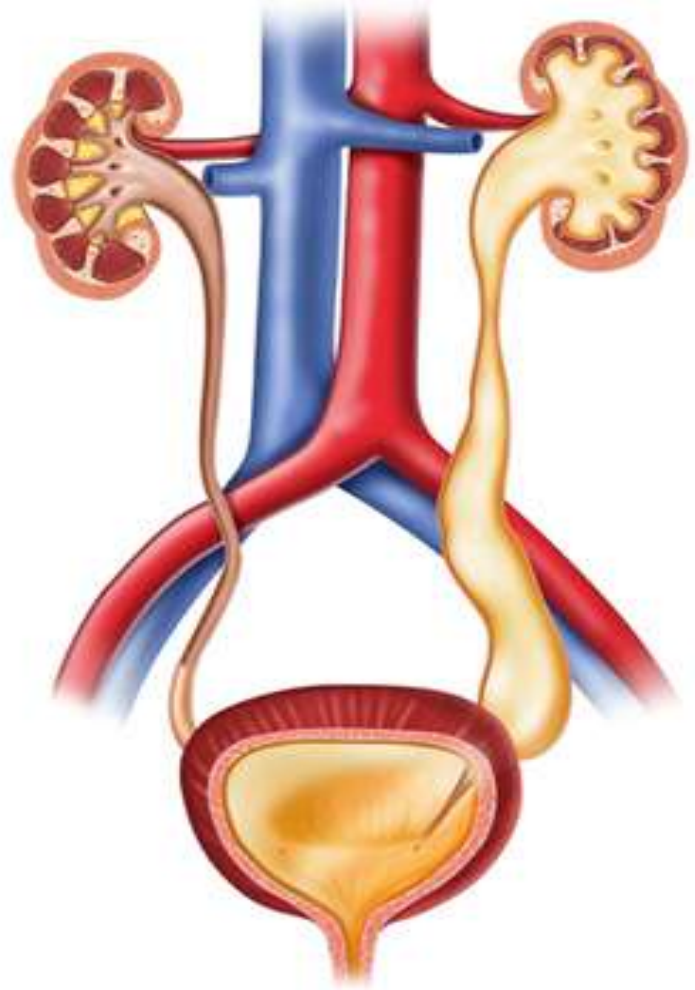
- The nitrosoureas (lomustine, carmustine, streptozocin) occasionally cause severe and progressive renal tubular damage.
- Tyrosine kinase inhibitors such as sunitinib and imatinib have been associated with various forms of kidney injury, including reduced glomerular filtration rate (GFR), proteinuria, and thrombotic microangiopathy

POSTRENAL ACUTE KIDNEY INJURY

Normal System



Uretrovesical Obstruction (UVJO)



- Intratubular obstruction due to uric acid (in TLS), methotrexate, or myeloma casts has been discussed earlier.



- Retroperitoneal fibrosis can be associated with previous pelvic irradiation or malignancies such as lymphomas and sarcomas

ELECTROLYTE DISORDERS

NA

K

CA

Mg





- Hypokalemia can result from gastrointestinal or kidney losses, with the latter most often due to tubular injury from ifosfamide or cisplatin.
- Tubular injury from these drugs can also cause long-term magnesium wasting and hypomagnesemia

ELECTROLYTE ABNORMALITIES

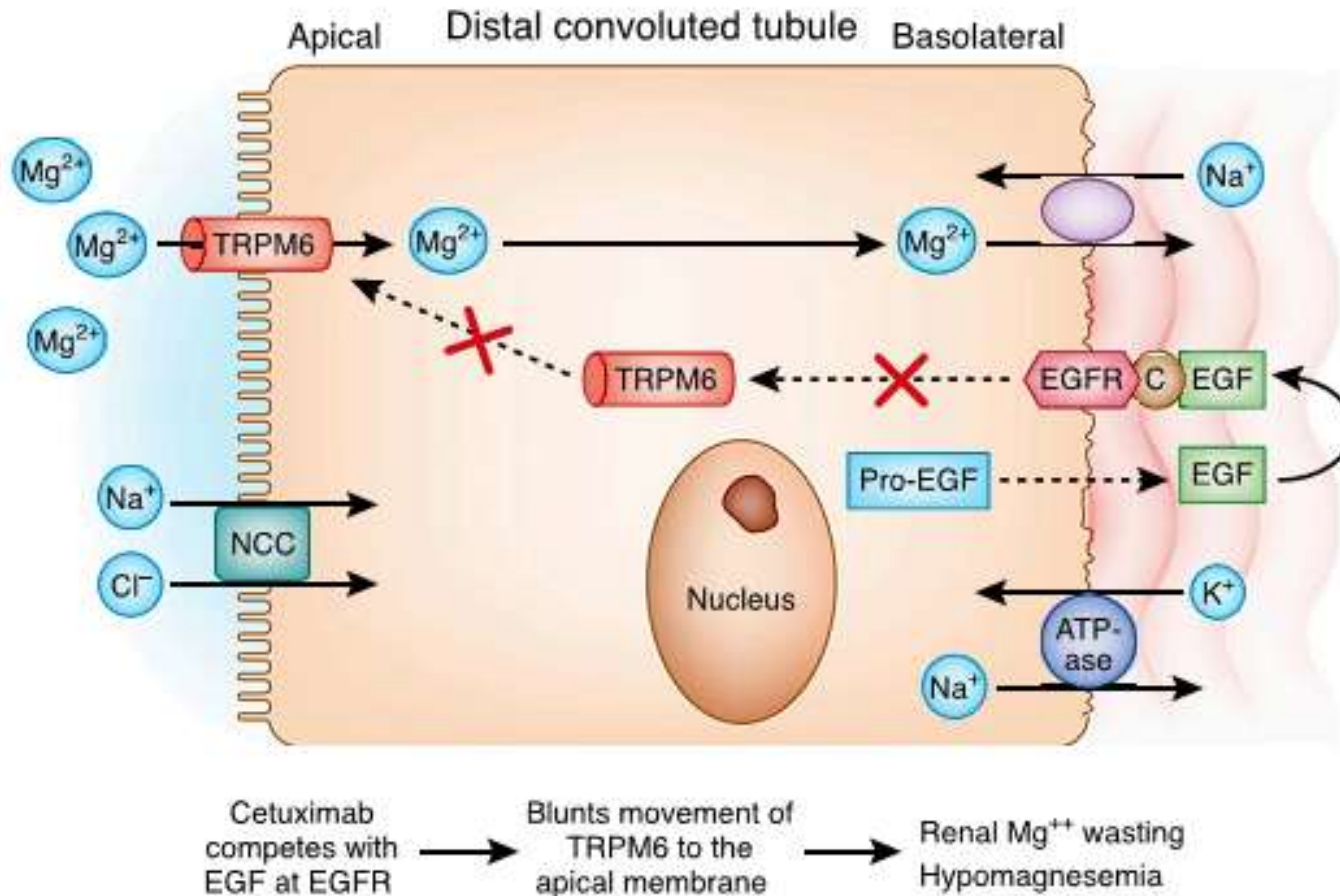
- **Imatinib** (mTKI) induces hypophosphatemia
 - inhibition of platelet-derived growth factor receptor expressed on osteoclasts
 - subsequent decreased bone resorption
 - decreased calcium, and phosphate egress from the bone
 - PTH levels (due to decreased calcium egress) and further renal phosphate wasting
- **Cetuximab/Panitumumab**-EGFR antibody
 - Hypomagnesemia-due to renal wasting
 - Possible inhibition of TRPM6 cation channel

Berman E., et al. N Engl J Med 2006;354:2006-13.

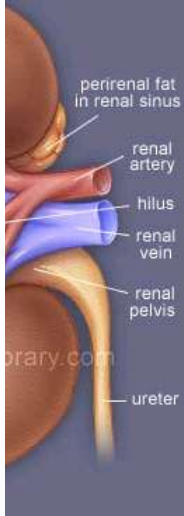
Schrag D., et al. JNCI, Vol. 97, No. 16, August 17, 2005



CETUXIMAB



Cetuximab (C) is an EGF receptor (EGFR) antibody that causes renal magnesium wasting by competing with EGF for its receptor. Normally, EGF binds its receptor (EGFR) and stimulates magnesium reabsorption in the distal convoluted cell. EGFR activation is associated with magnesium absorption through transient receptor potential M6 (TRPM6) in the apical membrane. NCC, sodium chloride cotransporter.



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Thank You
Thank You
Thank You!!!!